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EXAMINER	
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1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,008	CAO ET AL.	
	Examiner	Art Unit	
	Kimberly A. Makar, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

1. Amendments to claims 1 and 4 in the response dated 2/26/07 is acknowledged. Cancellation of claims 11-16 by applicant in the response dated 2/27/07 is acknowledged. Currently, claims 1-10 are pending. Any rejection not maintained in this office action is withdrawn.

2. The following rejection is necessitated by applicant's amendments dated 2/26/07. The amendment to claim 1 altered the scope of claim 1 such that the method for introducing a mutation into a target nucleotide sequence went from reading on a DNA with an inverted repeat sequence wherein the mutation was anywhere within the DNA, but now reads on a DNA with an inverted repeat sequence wherein the mutation specifically occurs within the inverted repeat region of the DNA.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claims 1, and 7-10 are rejected under 35 U.S.C. 102(e) as being anticipated by Graham (US Patent 6,573,099). Claims 1, 7-10 recite a method for introducing a mutation into a nucleotide sequence of a target nucleic acid, the method comprising the steps of: 1) preparing a DNA having an inverted repeat sequence, wherein the inverted repeat sequence comprises a sense strand sequence and an antisense strand sequence of a target nucleic acid and contains a mutation to be introduced into the target nucleic acid, wherein the sense strand sequence and the antisense strand sequence are arranged in tandem, and the mutation to be introduced into the target nucleic acid is located within the sense strand sequence and the antisense strand sequence in the inverted repeat sequence; and 2) transferring the DNA having an inverted repeat sequence into a cell. The method is further limited wherein the target is in the cytoplasm (claim 7) or in the nucleus (claim 8), and wherein a plurality of mutations are simultaneously introduced into the target nucleic acid (claim 9) wherein the mutation is a substitution, deletion, and/or insertion of a nucleotide (claim 10).

5. The preamble of the claims, "a method for introducing a mutation into a nucleic acid sequence of a target sequence" bears no patentable weight, as this appears to be the result a two step process comprising the preparation of a DNA sequence comprising an inverted repeat sequence that comprises the mutations, and transferring that DNA sequence into a cell. A preamble is generally not given any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness, but instead, the process steps or structural limitation are able to stand alone. See *In re Hirao*, 535

F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 197 F.2d 150, 152, 88 USPQ 578, 481 (CCPA 1951). Absent evidence to the contrary, any method which performs the same steps of preparing of a DNA sequence comprising an inverted repeat sequence that comprises mutations, and transferring that DNA sequence into a cell, teaches the same method.

6. Graham et al teaches a method of modifying gene expression in a cell by using nucleic acid vectors transferred into the cell. Graham teaches the preparation of the vectors which comprise inverted repeat sequences (synthetic structural genes), wherein the inverted repeat sequence comprises a sense strand and an antisense strand (see figures 14, 15, and 20). He teaches that the sense strand and the antisense strand of the inverted repeat sequences (synthetic structural genes) comprise mutations, including the deletion of start or stop codons, and "a gene of the invention may be subjected to mutagenesis to produce single or multiple substitutions, deletions and/or additions without affecting its ability to modify target gene expression" (column 5, lines 21-24). Graham teaches that the nucleic acids can be modified to include nucleic acid derivatives, including analogues including carbohydrates, radionucleotides, DIG, alkaline phosphatase, and horse radish peroxidase (column 5, lines 60-63). Graham teaches that the nucleic acids comprising the inverted repeat sequences comprise a head-to-head, head-to-tail, or tail-to-tail orientation of the inverted repeat region in tandem, and specifically teaches an embodiment of two repeated genes (column 10, lines 1-20; column 11, lines 9-16; and figures 14, 15, and 20). Graham teaches that the DNA comprising the inverted repeat sequences further comprises different regulatory

regions, including those which regulate spatial and temporal expression of the nucleic acid sequences (column 7, lines 44-48). Graham further teaches that the DNA encoding the inverted repeat sequences can be transferred as linear DNA or as a plasmid, viral vector, cosmid or artificial chromosome (column 13, lines 61-67) and that they can become integrated into the genome of the cell or organism (column 14, lines 6-11, and 42-47).

7. Graham teaches that the target genes are endogenous and exogenous genes including viral and foreign genes and those genes endogenous to the cell, tissue or organ (see abstract, as well as column 4, lines 40-45). Graham defines a gene as genomic sequences, mRNA, cDNA, antisense or recombinant DNA that has been introduced into the cell (column 4, lines 1-18). Thus the target genes that are genomic targets are inside the nucleus while mRNA and antisense sequences that are target sequences would be cytoplasmic.

8. Graham further teaches that the nucleotide sequences comprising the inverted repeat regions are prone to homologous recombination:

> For example, those skilled in the art will be aware of the inherent instability of palindromic nucleotide sequences in vivo and the difficulties associated with constructing long synthetic genes comprising inverted repeated nucleotide sequences, because of the tendency for such sequences to form hairpin loops and to recombine in vivo. Notwithstanding such difficulties, the optimum number of structural gene sequences to be included in the synthetic genes of the present invention may be determined empirically by those skilled in the art, without any undue experimentation and by following standard procedures such as the construction of the synthetic gene of the invention using recombinase deficient cell lines, reducing the number of repeated sequences to a level which eliminates or minimises recombination events and by keeping the total length of the multiple structural gene sequence to an acceptable limit, preferably no more than 5-10 kb, more preferably no more than 2-5 kb and even more preferably no more than 0.5-2.0 kb in length (column 10, lines 32-44).

9. Thus, Graham teaches that the palindrome vectors are subject to recombine. If the DNA target is an endogenous gene, the vector will recombine with the endogenous gene resulting in the introduction of the mutations of the target sequence from the inverted repeat region. Graham teaches the elimination or minimization of recombination as an option, not as a requirement. Finally Graham teaches that the DNA sequences comprising the inverted repeat regions are transferred into the cell (column 13, lines 57-67). Thus Graham teaches the claimed invention.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 5-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Graham (US Patent 6,573,099) and Robbins et al (Viral Vectors for Gene Therapy. Pharmacology, 1998. 80(1):35-47). Claims 5-6 recite a method for introducing a mutation into a nucleotide sequence of a target nucleic acid, the method comprising the steps of: 1) preparing a DNA having an inverted repeat sequence, wherein the inverted repeat sequence comprises a sense strand sequence and an antisense strand sequence of a target nucleic acid and contains a mutation to be introduced into the target nucleic acid, wherein the sense strand sequence and the antisense strand sequence are arranged in tandem, and the mutation to be introduced into the target

nucleic acid is located within the sense strand sequence and the antisense strand sequence in the inverted repeat sequence ; and 2) transferring the DNA having an inverted repeat sequence into a cell, wherein the DNA having the inverted repeat sequence is a double-stranded DNA (claim 5) or a single stranded DNA (claim 6).

12. Graham teaches a method for introducing a mutation into a nucleotide sequence of a target nucleic acid, the method comprising the steps of: 1) preparing a DNA having an inverted repeat sequence, wherein the inverted repeat sequence comprises a sense strand sequence and an antisense strand sequence of a target nucleic acid and contains a mutation to be introduced into the target nucleic acid, wherein the sense strand sequence and the antisense strand sequence are arranged in tandem, and the mutation to be introduced into the target nucleic acid is located within the sense strand sequence and that antisense strand sequence in the inverted repeat sequence ; and 2) transferring the DNA having an inverted repeat sequence into a cell (see above).

13. Graham teaches that the DNA can be an artificial chromosome, viral vector or plasmids (column 13 lines 61-67), but does not specifically teach that the DNA having the inverted repeat sequence is double-stranded or single stranded DNA.

14. Robbins et al (Viral Vectors for Gene Therapy. Pharmacology, 1998. 80(1):35-47) teaches that viral vectors are highly efficient at nucleic acid delivery to specific cell types while avoiding immunosurveillance by an infected host (see abstract). Robbins teaches that adenoviral vectors are double stranded linear DNA viruses that are widely used for gene delivery in vivo and are used in clinical trials. Adenoviral vectors have the advantage of infecting some nondividing cells, resulting in high levels of transient gene

expression (page, 37, column I, last paragraph). Robbins teaches that Adeno-associated virus (AAV) vectors are also used as delivery vehicles. Robbins teaches that AAV vectors are single stranded DNA viruses "appear to be an excellent gene transfer vehicle for delivery of genes smaller than 5kb to muscle or neuronal cells" (page 40, columns I and II).

15. It would have been obvious to modify the generic viral vector of the DNA having the inverted repeat region taught by Graham and combine it with the teaching of Robbins on single-stranded or double-stranded nucleic acid viral vectors in order to more efficiently transfer the mutation construct. A skilled artisan would have been motivated to combine the teaching of Graham on using viral vectors to deliver his construct further with the teaching of Robbins on well-known Adenoviral and Adeno-Associated viral vectors as highly efficient vectors for transferring nucleic acids and make either single stranded or double stranded DNA constructs comprising the inverted repeat region so to efficiently transfer the constructs taught by Graham. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the instant invention was made, it must be considered that said ordinary skilled artisan would have had reasonable expectation of success in practicing the claimed invention.

16. Claims 2-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Graham (US Patent 6,573,099) as applied to claim 1 above, further in view of Dean (US Patent No: 6,130,207) (of record 11/30/06). Claims 2-3 recite a method for introducing a mutation into a nucleotide sequence of a target nucleic acid, the method comprising the steps of: 1) preparing a DNA having an inverted repeat sequence, wherein the

inverted repeat sequence comprises a sense strand sequence and an antisense strand sequence of a target nucleic acid and contains a mutation to be introduced into the target nucleic acid, wherein the sense strand sequence and the antisense strand sequence are arranged in tandem, and the mutation to be introduced into the target nucleic acid is located within the sense strand sequence and the antisense strand sequence in the inverted repeat sequence; and 2) transferring the DNA having an inverted repeat sequence into a cell, wherein the DNA having an inverted repeat sequence has a binding motif sequence for a protein having a nuclear transport signal (claim 2) and that specific binding motif is for a transcription factor binding motif (claim 3).

17. Graham teaches a method for introducing a mutation into a nucleotide sequence of a target nucleic acid, the method comprising the steps of: 1) preparing a DNA having an inverted repeat sequence, wherein the inverted repeat sequence comprises a sense strand sequence and an antisense strand sequence of a target nucleic acid and contains a mutation to be introduced into the target nucleic acid, wherein the sense strand sequence and the antisense strand sequence are arranged in tandem, and the mutation to be introduced into the target nucleic acid is located within the sense strand sequence and that antisense strand sequence in the inverted repeat sequence ; and 2) transferring the DNA having an inverted repeat sequence into a cell (see above). Graham further teaches that the DNA sequence comprising the inverted repeat sequence can be modified to comprise different regulatory sequences, such as different promoters and terminators, which give spatial and temporal control to the expression of

the DNA sequences (column 7, lines 44-48). Graham further teaches that the DNA sequence of his invention can be "advantageous in modifying target gene expression in cells, tissue or organs of a prokaryotic or eukaryotic organism" (column 4, lines 35-39) thus suggesting the use of these vector for gene therapy purposes. Graham does not teach that the DNA comprising the inverted repeat region comprises a binding site that would target the DNA into the nucleus, nor that it is specific for a transcription factor.

18. Dean et al (US Patent No: 6,130,207) teaches a plasmid comprising a DNA binding sequence specific for transcription factors (column 2, lines 54-67). Dean teaches that the binding sites allow transcription factors to bind to the plasmid and import the plasmid into the nucleus, thereby allowing the DNA to utilize the transcription factor nuclear localization signal for nuclear import (column 2, lines 54-67). Dean teaches that the binding sites can be for transcription factors such as AP1, Ap4, and Sp1 (column 3, lines 3-8). Dean teaches that the DNA to be imported into the nucleus can be flanked by IR sequences (column 8, lines 31-50). Dean teaches the DNA insert integrates into the host genome through homologous recombination at homologous sequences (column 11, lines 2—24). Dean further teaches that two problems hindering gene therapy are, "(1) gene transfers to non-diving cells are still extremely inefficient and (2) gene transfer to specific desired non-dividing cells within a population of other cell types is even more inefficient. Thus any way to increase the amount of gene transfer will greatly benefit this emerging field" (column 1, lines 18-22) and in order to fully exploit the potential for gene therapy, there is a "continuing need for ways to increase the amount of gene transfer to cells" (column 1, lines 64-67). Dean teaches

that his invention, a plasmid comprising a cell-specific nuclear targeting molecule comprising a transcription factor binding motif meets this need (column 2, lines 5-27).

19. A skilled artisan would have been motivated to combine the teaching of Graham on a method for introducing a mutation into a nucleotide sequence of a target nucleic acid, the method comprising the steps of: 1) preparing a DNA having an inverted repeat sequence, wherein the inverted repeat sequence comprises a sense strand sequence and an antisense strand sequence of a target nucleic acid and contains a mutation to be introduced into the target nucleic acid, wherein the sense strand sequence and the antisense strand sequence are arranged in tandem, and the mutation to be introduced into the target nucleic acid is located within the sense strand sequence and the antisense strand sequence in the inverted repeat sequence; and 2) transferring the DNA having an inverted repeat sequence into a cell, where Graham specific teaches modification of the DNA with inverted sequences with different regulatory regions that control spatial and temporal control with the teaching of Dean that transcription factor binding regions on plasmids aid in transporting vectors into the nucleus because the addition of the transcription factor binding sites to the nucleic acid sequences of Graham would increase the overall efficiency of transport of the sequences into the nucleus, thereby increasing the modification of endogenous genes. It would have been obvious to the skilled artisan to combine the teaching of Graham with the teaching of Dean, because the addition of the transcription binding site to the modular DNA inverted repeat nucleic acid sequences of Graham would have increased the reliability and modification of genes as taught by the Graham method. Given the teachings of the prior

art and the level of skill of the ordinary skilled artisan at the time the instant invention was made, it must be considered that said ordinary skilled artisan would have had reasonable expectation of success in practicing the claimed invention.

20. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Graham (US Patent 6,573,099) as applied to claim 1 above, further in view of Wengel et al (WO 99/14226) (of record 12/30/04). Claim 4 recites a method for introducing a mutation into a nucleotide sequence of a target nucleic acid, the method comprising the steps of: 1) preparing a DNA having an inverted repeat sequence, wherein the inverted repeat sequence comprises a sense strand sequence and an antisense strand sequence of a target nucleic acid and contains a mutation to be introduced into the target nucleic acid, wherein the sense strand sequence and the antisense strand sequence are arranged in tandem, and the mutation to be introduced into the target nucleic acid is located within the sense strand sequence and the antisense strand sequence in the inverted repeat sequence; and 2) transferring the DNA having an inverted repeat sequence into a cell, wherein the DNA having an inverted repeat sequence is has a modified nucleotide selected from the group consisting of a methylated ribonucleotide, a sulfurized deoxynucleotide and an LNA.

21. Graham teaches a method for introducing a mutation into a nucleotide sequence of a target nucleic acid, the method comprising the steps of: 1) preparing a DNA having an inverted repeat sequence, wherein the inverted repeat sequence comprises a sense strand sequence and an antisense strand sequence of a target nucleic acid and contains a mutation to be introduced into the target nucleic acid, wherein the sense

strand sequence and the antisense strand sequence are arranged in tandem, and the mutation to be introduced into the target nucleic acid is located within the sense strand sequence and the antisense strand sequence in the inverted repeat sequence; and 2) transferring the DNA having an inverted repeat sequence into a cell (see above). Graham teaches that his invention is capable of homologous recombination, and is used for the purpose of modifying gene expression (see above). Graham further teaches the nucleic acids can be modified to include nucleic acid derivatives, including analogues compising carbohydrates, radionucleotides, DIG, alkaline phosphatase, and horse radish peroxidase (column 5, lines 60-63). However Graham does not teach that the analogue nucleotides are modified nucleotides selected from the group consisting of a methylated ribonucleotide, a sulfurized deoxynucleotide and an LNA.

22. Wengel et al discloses the use of LNAs of his invention improve the "affinity and specificity towards complementary RNA and DNA oligomers" (see abstract). Wengel teaches that his LNAs are useful for preparing oligomers (page 37). Wengel teaches that the LNAs of his invention have surprisingly good hybridization properties with a substantially higher 3'exonucleolytic stability than unmodified oligonucleotides (page 46-48). Wengel further teaches that his LNAs are useful in modifying gene expression via antisense and therapeutic strategies (see abstract and introduction).

23. A skilled artisan would have been motivated to combine the teaching of Graham on a method of modifying the expression of a gene by introducing a mutation into a nucleotide sequence of a target nucleic acid, the method comprising the steps of: 1) preparing a DNA having an inverted repeat sequence, wherein the inverted repeat

sequence comprises a sense strand sequence and an antisense strand sequence of a target nucleic acid and contains a mutation to be introduced into the target nucleic acid, wherein the sense strand sequence and the antisense strand sequence are arranged in tandem, and the mutation to be introduced into the target nucleic acid is located within the sense strand sequence and the antisense strand sequence in the inverted repeat sequence; and 2) transferring the DNA having an inverted repeat sequence into a cell with the teaching of Wengel on the increased binding affinity and stability of the LNA nucleotides useful in antisense and therapeutic methodologies, because the use of Wengel's LNAs would improve the method of Graham by increasing the stability of the DNA comprising the inverted repeat sequence once transferred into the target cell, and increase the binding of the DNA to the corresponding target sequence, thereby increasing the specificity and modification of Graham's method. It would have been obvious to the skilled artisan to combine the teaching of Graham on modifying gene expression using a construct with an inverted repeat region with the teaching of Wengel because Graham specifically teaches the incorporation of additional nucleotide analogues that would aid in his method, and Wengel provides nucleotide analogues which would improve the efficiency and results of Graham's method. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the instant invention was made, it must be considered that said ordinary skilled artisan would have had reasonable expectation of success in practicing the claimed invention.

Conclusion

24. No claims are allowed.

25. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Makar, Ph.D. whose telephone number is 571-272-4139. The examiner can normally be reached on 8AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D. can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kam/5/16/07

D Sullivan

Daniel M. Sullivan
Primary Examiner